PRotocolised Evaluation of permiSSive blood pressure targets versus Usual caRE (PRESSURE)

Chief Investigator: Dr David Inwald

Site Initiation Visit
Agenda

• Background
• Objectives
• Trial Design
• Eligibility
• Screening & Enrolment
• Randomisation

• Consent
• Local Resource
• Governance
• Case Report Forms
• Safety
• Next steps
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Background

• In critically ill children, hypotension (low blood pressure) is common, especially in patients with severe infections and is a key feature of shock. Severe hypotension may compromise tissue perfusion and organ function, with a risk of multiple organ failure

• Vasoactive agents (which also stimulate the heart) and fluids are mainstays of treatment

• Though interventions to treat hypotension may be lifesaving, there are also harms. Excessive fluids are associated with increased morbidity and mortality. Most vasoactive drugs induce vasoconstriction, which may reduce blood flow and organ function
• Current guidelines recommend maintaining mean arterial pressure (MAP - mean arterial pressure) for children with sepsis around the 50th centile for age. These guidelines are based on low quality evidence and no guidance is given for an upper MAP limit.

• The PRESSURE trial will test the hypothesis that the benefits associated with a lower blood pressure target in critically ill children will outweigh risks associated with lower MAP values and the medical interventions needed to raise blood pressure, improving outcomes and decreasing costs.
Aim

To evaluate the clinical and cost-effectiveness of a permissive blood pressure target (MAP target of 5\textsuperscript{th} centile for age), to guide treatment (as compared with usual care) in critically ill children with hypotension.

Research Question

- **Population**  Mechanically ventilated critically ill children receiving vasoactive drugs for hypotension
- **Intervention** Permissive blood pressure target (MAP target 5\textsuperscript{th} centile for age) in order to minimise dose and duration of medical interventions
- **Comparator**  Usual care
- **Outcome**  Composite outcome of mortality and duration of ventilator support at 30 days
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Objectives

Primary Objectives

Evaluate:

- Composite outcome of mortality and duration of ventilator support at 30 days (clinical effectiveness)

- Incremental costs, quality-adjusted life years (QALYs) at 12 months (cost effectiveness)
Objectives

Secondary Objectives

Evaluate:

- Mortality at PICU discharge, 30 days, 90 days and 12 months
- Duration of survival to 12 months
- Time to liberation from invasive ventilation
- Functional status at PICU discharge and at 1 year.
- Length of PICU and hospital stay
- Health-related quality of life (HrQoL) at 1 year
- Incremental costs at 30 days
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Trial Design

- Pragmatic, multi-centre, parallel group randomised clinical trial
- 1900 patients
- 17 paediatric critical and intensive care units (PICUs) and associated PICU retrieval services
- 30-month recruitment period (August 2021-Feb 2024)
- Each participant will be followed up with a questionnaire at 12 months post randomisation to assess HrQoL
- Internal pilot - traffic light progression criteria in first six months of recruitment period
Intervention

Permissive Blood Pressure Target

- Those patients randomised to permissive blood pressure will be allocated their target range based on age (5th centile MAP threshold to 5th centile MAP threshold + 5 mmHg)

<table>
<thead>
<tr>
<th>Age range (completed months/years)</th>
<th>Target range</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than 6 months</td>
<td>40 - 43</td>
</tr>
<tr>
<td>6 months – less than 1 year</td>
<td>40 - 45</td>
</tr>
<tr>
<td>1 - 3 years</td>
<td>45 - 50</td>
</tr>
<tr>
<td>4 - 9 years</td>
<td>50 - 55</td>
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<tr>
<td>≥10 years</td>
<td>55 - 60</td>
</tr>
</tbody>
</table>

- MAP should be within range whilst receiving vasoactive drugs
• Decision to discontinue vasoactive drugs depends on ability to maintain MAP above the 5<sup>th</sup> centile threshold without vasoactive drugs

• Permissive blood pressure range will apply if the patient requires vasoactive drugs whilst on PICU, including readmission from another inpatient area

• Vasoactives should only be restarted if MAP is lower than the 5<sup>th</sup> centile threshold
• Post extubation, if vasoactives are restarted 5<sup>th</sup> centile threshold should apply

• If patient develops exclusion criterion after randomisation, treating clinician’s discretion as to whether the permissive blood pressure target range is continued
Usual Care

- Patients in the control arm will receive usual care (as per local practices)

- Usual care will apply at any point the patient requires vasoactive drugs whilst on PICU during the acute hospital admission, including readmissions to PICU from another inpatient care area
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Eligibility

Inclusion Criteria

• Age >37 weeks corrected gestational age and <16 years

• Accepted for or admitted to PICU

• Receiving a continuous infusion of vasoactive drug for hypotension commenced within previous 6 hours

• Vasoactive drug expected to continue for at least 6 hours or more

• On invasive mechanical ventilation
Exclusion Criteria

- Admitted post cardiac surgery
- Known cardiomyopathy
- Neonates with suspected or proven duct dependent circulation
- Brain injury
- Pulmonary hypertension
- Malignant hypertension
- Death perceived as imminent
- Previously recruited to PRESSURE
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Screening and Enrolment

- Screening and Enrolment Log - Excel spreadsheet

- Record all patients who are:
  - Accepted for or admitted to PICU
  - Receiving vasoactive drugs

- Which will include
  - eligible patients randomised
  - eligible patients not randomised
  - patients meeting one or more exclusion criteria

See SOP 003 - Patient screening and enrolment
Screening and Enrolment Log

- Each row on the spreadsheet represents a patient

- Section A: Child details

<table>
<thead>
<tr>
<th>Hospital Number/Local Identifier (remove prior to submission to ICNARC)</th>
<th>Start of vasoactive drugs (dd/mm/yy)</th>
<th>Start of vasoactive drugs (hh:mm)</th>
<th>Date of screening (dd/mm/yy)</th>
<th>Time of screening (hh:mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>
Screening and Enrolment Log

- **Section B: Inclusion criteria**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;37 weeks corrected gestational age to ≤16 years</td>
</tr>
<tr>
<td>Accepted for or admitted to PICU</td>
</tr>
<tr>
<td>Receiving a continuous infusion of vasoactive drug for hypotension commenced</td>
</tr>
<tr>
<td>within previous 6 hours</td>
</tr>
<tr>
<td>Vasoactive drug expected to continue for at least 6 hours or more</td>
</tr>
<tr>
<td>On invasive mechanical ventilation</td>
</tr>
</tbody>
</table>

- **Section C: Exclusion criteria**

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admitted post cardiac surgery</td>
</tr>
<tr>
<td>Known cardiomyopathy</td>
</tr>
<tr>
<td>Neonates with suspected or proven duct dependent circulation</td>
</tr>
<tr>
<td>Brain injury</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Malignant hypertension</td>
</tr>
<tr>
<td>Death perceived as imminent</td>
</tr>
<tr>
<td>Previously recruited to PRESSURE</td>
</tr>
</tbody>
</table>
Screening and Enrolment Log

- Section D: Screening outcome

<table>
<thead>
<tr>
<th>Screening outcome</th>
<th>Trial number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised (Complete Section F)</td>
<td></td>
</tr>
<tr>
<td>Identified after 6h time-window (detail in Comment)</td>
<td></td>
</tr>
<tr>
<td>Not randomised - Met ≥1 exclusion criteria</td>
<td></td>
</tr>
<tr>
<td>Eligible not randomised (Complete Section E)</td>
<td></td>
</tr>
<tr>
<td>Not randomised - Eligibility unknown</td>
<td></td>
</tr>
</tbody>
</table>

- Spreadsheet set up to indicate which fields should/should not be completed based on selection
Screening and Enrolment Log

- Section E and Section F (complete as appropriate)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Section E</th>
<th>Section F</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If eligible but not randomised, (select reason and explain in Comments section)</td>
<td>Is patient enrolled in other studies? If yes, please list which studies</td>
<td></td>
</tr>
</tbody>
</table>

- Co-enrolment
  - Consider co-enrolment with PRESSURE on a study-by-study basis
  - If participating in Oxy-PICU please consider all patients that are not on vasoactive drugs for randomisation to Oxy-PICU
Screening and Enrolment Log

- Submit regularly to ICNARC CTU
- e.g. fortnightly
- email to pressure@icnarc.org

Do not include any identifiable information when submitting the Log
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Randomisation

Web randomisation
- Email pressure@icnarc.org to request account
- https://www.sealedenvelope.com/access

Telephone randomisation
- Study number for PRESSURE 2996
- 3-digit investigator number for each site (is also start of trial ID)

- Trained staff on delegation log, GCP not required

See SOP 004 - Patient Randomisation
Randomisation Form

Eligibility check

Inclusion - all must be yes
- Age >37 weeks corrected gestational and <16 years
- Accepted for or admitted to PICU
- Receiving a continuous infusion of vasoactive drug for hypotension commenced within previous 0 hours
- Vasoactive drug expected to continue for 6 hours or more
- On invasive mechanical ventilation

Exclusion - all must be no
- Admitted post cardiac surgery
- Known cardiomyopathy
- Neonates with suspected or proven duct dependent circulation
- Brain injury
- Pulmonary hypertension
- Malignant hypertension
- Death perceived as imminent
- Previously recruited to PRESSURE

*Please Note: If the patient is not on vasoactive drugs, please consider them for ICU/PICU

If all inclusion criteria are "Yes" and all exclusion criteria are "No" dial: XXX XXXX XXX

Study number: XXX Investigator number: XXX
or log on to: https://wwwsealedenvelope.com/access

How to randomise

Details required by randomisation service

Confirmation of randomisation

Sign off by trained staff member
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Consent

- Deferred consent

- The clinical/research nurse team will approach the parents/legal guardians as soon as practically possible and appropriate to discuss trial & provide participant documentation:
  - Parent / Legal Guardian Information Sheet (associated bereaved versions)
  - Parent / Legal Guardian Consent Form (associated bereaved versions)
  - Age appropriate Information Sheets
  - Assent Forms
# Protocolised Evaluation of permissSive blood pressure targets versus Usual care

## Consent Form - Parent or Legal Guardian,

Version 1.0, 10 February 2021

### To be completed by the Researcher:

- **Hospital name:**
- **Trial ID:**
- **Child's full name:**

### To be completed by the Parent or Legal Guardian:

Once you have read and understood each statement – **if you agree, please write your initials in each box**

1. **I confirm that I have read and understood the Participant Information Sheet (version 1.0, 10 Feb 2021) for the above research study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.**

2. **I understand that participation is voluntary, and that I am free to withdraw consent at any time, without giving any reason and without my child's medical care or legal rights being affected.**

3. **I agree for my child to continue to take part in this study.**

4. **I agree for the Hospital NHS Trust research team to access my child's medical records and collect and send the full anonymised dataset securely to the Intensive Care National Audit and Research Centre (ICNARC) which is coordinating the study.**

5. **I agree that identifiable data related to my child (including name, date of birth, postcode and NHS number), may be processed by individuals from ICNARC, NHS Digital or NHS Wales Informatics Service where it is relevant to the participation in this research.**

6. **I agree that my child’s medical records, held by the NHS, may be looked at by authorised individuals from ICNARC, the Sponsor or regulatory authorities to check that the study is being carried out correctly.**

7. **I agree for ICNARC to send me a questionnaire to find out how my child is doing in one year’s time.**

8. **I agree that the information collected in the study will be used to support other research in the future, and may be shared anonymously with other researchers.**

9. **I would like to be contacted about any future related studies.**
Consent Guidance

Check timing is appropriate:
- Parents happy to be approached once child is stable and after initial stress
- Consult nursing staff about child’s condition and their views on how parents are coping
- Bereaved - if appropriate in hospital

- Provide information
- Allow time to read information sheet
- Invite/encourage questions
- Confirm decision
- Where possible, assent from patient should be obtained prior to discharge
Discharge prior to consent

- At least one phone call
- Personalised cover letter, PIS, Consent Form posted
- If no response after four weeks, a follow up letter, PIS, Consent Form posted
- If nothing received within four weeks participant included
Non-consent / Withdrawal

- If parent/guardian withdraws consent at any time or refuses to give consent (‘non-consent’) their decision must be respected.

- All data up to the point of withdrawal will be retained and a minimised anonymised dataset will be collected and retained for monitoring safety and important trial outcomes (unless explicit requests otherwise).

- To monitor non-consent, details should be added to MACRO.
Bereaved Consent

- Site research team should work with colleagues/bereavement counsellors to establish whether the approach to obtain consent is appropriate before they leave hospital.

- If deferred consent is not sought prior to departure, covering letter, bereaved-PIS and bereaved Consent Form to be posted (four weeks after randomisation).

- If no response after four weeks, a follow up letter, bereaved-PIS, bereaved- Consent Form posted.

- If no response in four weeks participant included.
Protocolised Evaluation of permisSSive blood pressure targets versus Usual care
Consent Form - Parent or Legal Guardian
Version 1.0, 10 February 2021

To be completed by the Researcher:
Hospital name: [ ]
Trial ID: [ ]
Child's full name: [ ]

To be completed by the Parent or Legal Guardian:
Once you have read and understood each statement – if you agree, please write your initials in each box

1. I confirm that I have read and understood the Participant Information Sheet (Version 1, 10 Feb 2021) for the above research study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. [ ]

2. I understand that participation is voluntary, and that I am free to withdraw consent at any time, without giving any reason and without my legal rights being affected. [ ]

3. I agree for the Hospital NHS Trust research team to access my child's medical records and collect and send the full anonymised dataset securely to the Intensive Care National Audit and Research Centre (ICNARC) which is coordinating the study. [ ]

4. I agree that my child's medical records, held by the NHS, may be looked at by authorised individuals from ICNARC, the Sponsor, or regulatory authorities to check that the study is being carried out correctly. [ ]

5. I agree that the information collected in the study will be used to support other research in the future, and may be shared anonymously with other researchers. [ ]

6. I agree for my contact details to be sent to ICNARC for any future related studies. [ ]

Your signature: [ ] Date: [ ]
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Local Resources

- Site research team led by PI
- Local document pack and ISF documents provided electronically
- Direct research costs from ICNARC
  - £1000 Start up (including the recruitment of a patient)
  - £185 ppp
  - £500 close-down

Invoices should be submitted quarterly in arrears to accounts@icnarc.org

Invoices must have a PO number obtained from pressure@icnarc.org
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Governance - Central

- Sponsor: Cambridge University Hospitals NHS Foundation Trust
- Clinical Trials Unit: ICNARC CTU
- Ethics: East of England - Cambridge South Research Ethics Committee (Ref: 21/EE/0084)
  - Favourable ethical opinion: 10 May 2021
- HRA/HCRW Approval (IRAS number: 289545)
  - Approval: 10 May 2021
- NIHR CPMS ID: 128895
- ISRCTN Registry ID: ISRCTN20609635
Governance - Local

- Local confirmation of capacity and capability
  - Local site document packs sent

- Site responsibilities/activation
  - Signed Clinical Trial Site Agreement
  - Local C&C
  - Delegation Log and Staff Contacts Form
  - GCP certificate / CVs
  - Acknowledgment statements

- All needed prior to site activation
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Case Report Forms

- Randomisation Form
- Baseline - Demographics / Observations
  - Comorbidites
  - Functional status prior to PICU admission
- Observations
- Daily Values
- Organ support daily observations
- Outcomes - Functional status at PICU discharge
  - At hospital discharge
  - Survival status
- Consent/Assent
- Safety Monitoring
- SAE Reporting Form

See SOP 007 - Guidance for completion of Case Report Forms for further details
Site Initiation Visit
e-CRF

- Secure web-based data entry system (MACRO):
  - [https://ctu.icnarc.org/macro/](https://ctu.icnarc.org/macro/)
  - Full audit trail - all changes to data are recorded against a named user

- Email pressure@icnarc.org to set-up an account
  - Individual must be listed on Delegation Log

- Data should be entered promptly

- Training to follow
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Safety Monitoring

- From randomisation until PICU discharge

- Adverse Events (AEs)
  Specified (expected)
  - myocardial ischaemia
  - arrhythmia
  - digital or limb ischaemia
  - central line related blood stream infection
  - thrombus related to central line insertion
  - Skin necrosis related to administration of vasoactives via peripheral line
  - Severe acute renal failure (KDIGO stage 3 criteria)

Other (unspecified / unexpected) - only reported if considered to be possibly, probably or definitely related to the study treatment (blood pressure or vasoactive drug administration)
Safety Monitoring

- Serious Adverse Events (SAEs)
  - If severity of AE is severe, life-threatening or fatal
  - Report on SAE Reporting Form
  - Upload to MACRO
  - ICNARC CTU must be informed within 24 hours of the site team becoming aware of the event
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Next steps

• First sites able to recommence recruitment from November 2021

• Ensure confirmation of capacity and capability in place

• Return relevant sites responsibility / activation documents

• Complete MACRO training & set up access

• .....commence screening / recruitment!
ICNARC CTU PRESSURE Team

Email: pressure@icnarc.org

Tel: 020 4514 6248 (Alanna Brown)
    020 7831 6878 (Raul Szekely)

https://www.icnarc.org/Our-Research/Studies/Current-Studies/Pressure
Any questions?